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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/634,740	08/05/2003	Alice Y. Ting	M00656.70097.US	8302

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EXAMINER

MONDESI, ROBERT B

ART UNIT	PAPER NUMBER
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1653

DATE MAILED: 08/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

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Office Action Summary

Application No.

10/634,740

Applicant(s)

TING, ALICE Y.

Examiner

Robert B. Mondesi

Art Unit

1653

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 16 June 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 21-32, 34-36, 38, 40-45, 130 and 131 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 21-32, 34-36, 38, 40-45 and 130-131 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 05 August 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- ☒ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- ☐ Notice of Informal Patent Application (PTO-152)
- ☐ Other: _____

DETAILED ACTION

This Office action is in response to the amendment filed June 3, 2005. **Claims 21-32, 34-36, 38, 40-45 and 130-131** are presently pending and under examination.

New Objection(s) and Rejection(s)

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21-32, 34-36, 38, 40-45 and 130-131 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In **claim 21**, it is not clear as to what the nature relationship between the amount of FRET and the level of histone "covalent" modification is supposed to be. Is there a standard curve of FRET that correlates with the level of histone "covalent" modification? What is presently being monitored is a relative FRET level and therefore presumably a relative histone "covalent" modification level. The claim is unclear with regards to whether FRET goes up or does with increased "covalent" modification. **Claims 21-32, 34-36, 38, 40-45 and 130-131** are dependent claims that do not remedy the deficiencies of the rejected base claim that they are dependent upon.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 21-32, 34-36 40-45 and 130-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Craig et al., United States Patent No: 6,465,199 in view of Akhtar et al., 2000.

Independent **claim 21**, which all other claims depend from has been amended to include the term "covalent". It is important to note that the applicants have defined covalent modification in the specification of the present application on page 44, lines 12-18 to be; phosphorylation, acetylation, methylation, ubiquitination, or ADP-ribosylation.

Craig et al. teach that an aspect invention is an isolated natural binding domain and a binding partner therefor, wherein the isolated natural binding domain includes a site for post-translational modification and binds the binding partner therefor in a manner dependent upon modification of the site.

Craig et al. also teach that the invention additionally encompasses a method for monitoring activity of an enzyme comprising performing a detection step to detect binding of an isolated natural binding domain and a binding partner therefor as a result of contacting one or both of the isolated natural binding domain and the binding partner

with the enzyme, wherein the isolated natural binding domain includes a site for post-translational modification and binds the binding partner in a manner dependent upon modification of the site and wherein detection of binding of the isolated natural binding domain and the binding partner as a result of the contacting is indicative of enzyme activity (column 4, lines 30-45).

Craig et al. teach further that another aspect of the invention is a method for monitoring activity of an enzyme comprising performing a detection step to detect dissociation of an isolated natural binding domain from a binding partner therefor as a result of contacting one or both of the isolated natural binding domain and the binding partner with said enzyme, wherein the isolated natural binding domain includes a site for post-translational modification and binds the binding partner in a manner dependent upon modification of the site and wherein detection of dissociation of the isolated natural binding domain from the binding partner as a result of the contacting is indicative of enzyme activity.

Craig et al. teach that the invention provides reporter molecules and assays for measuring the activity of protein modifying enzymes. These reporter molecules are naturally-occurring polypeptides which include natural binding domains, natural binding sequences and natural binding polypeptides, each as defined above, which are used in assays of the invention in combination with polypeptide binding partners, also as defined above and by monitoring the association or dissociation of a natural binding domain, sequence or polypeptide and its binding partner in the presence of a known or candidate protein modifying enzyme, the activity of such an enzyme can be measured.

Furthermore in such assays, one or both of the natural binding domain, sequence or polypeptide and its binding partner comprises a detectable label including, but not exclusively, a fluorescent or other light-emitting label, which may be either chemical or proteinaceous. By measuring changes in signal emission before and after addition to the mixture comprising the natural binding domain, sequence or polypeptide and its binding partner of the enzyme to be assayed, the extent of modification can be calculated. An important feature of the invention is that such measurements (e.g., of a shift in FRET or other signal emitted by a detectable label) can be performed in real-time. This allows for sensitive assessment of enzyme reaction kinetics based upon the rate of change of the protein-binding-dependent signal emission or absorption by the label(s)(Column 14, lines 1-25).

Most importantly Craig et al. teach that the term "modification" or "post-translational modification" refers to the addition or removal of a chemical "moiety", as described herein, to/from a site on a polypeptide chain and does not refer to other post-translational events which do not involve addition or removal of such a moiety as described herein, and thus does not include simple cleavage of the reporter molecule polypeptide backbone by hydrolysis of a peptide bond, but does include hydrolysis of an isopeptide bond (e.g., in the removal of ubiquitin) and **the terms "moiety" and "group" refer to one of the post-translationally added or removed groups referred to herein: i.e., one of a ubiquitin moiety, a glycosyl moiety, a fatty acyl moiety, a sentrin moiety or an ADP-ribosyl moiety** (Column 5, lines 36-55).

On page 15 of the specification the applicants state that examples of modification specific binding polypeptides for detecting phosphorylation modification are known in the art as evidenced by Fu et al. and Aitken et al. (14-3-3 domains) and Yaffe et al. (FHA or WW domains). The applicants state further that examples of modification-specific binding polypeptides for detecting protein acetylation include bromodomains (GCN5, P/CAF, CBP, BRG1, Swi2) are known in the art as evidenced by the following publications *FEBS Lett* 513 (1): 124-8 (2002), *Front Biosci* 6:D1019-23 (2001) and *Nat Struct Biol* 6(7):601-4 (1999)); and examples of modification-specific binding polypeptides for detecting methylation include chromo-domains (HP1, MRG-5, CHD5 and Swi6) which are also well known in the art as evidenced by *nature* 407(6802):405-9 (2000).

Craig et al. do not teach that the stated method above comprises fusion proteins comprising a histone modification specific binding domain wherein the histone polypeptide that is acetylated is a H4 histone polypeptide.

Akhtar et al. disclose a histone polypeptide that is H4 polypeptide and is acetylated at lysine 16 by the histone acetyltransferase.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use a H4 histone polypeptide in a fusion protein reporter construct as a histone modification specific binding domain in a method of determining the level of histone modification in a biological sample using FRET for the advantages of an acetylation reporter as taught by Aktar et al. and Craig et, see Aktar et al. page 408 and Craig et al., Column 4, lines 24-25).

Conclusion

No claims are allowed

Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.


Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert B. Mondesi whose telephone number is 571-272-0956. The examiner can normally be reached on 9am-5pm, Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Art Unit: 1653

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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08-16-05


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PRIMARY EXAMINER